Please rewrite claims 2-4 as new claims 41-43 as follows:

41. The method of claim 40 wherein the biological material is a cell.

42. The method of claim 40 wherein the biological material is an oocyte.

43. The method of claim 40 wherein the biological material is an embryo.

REMARKS

The claims have been amended in order to avoid the Examiner's rejection of claims 1-4 and 9 under 35 U.S.C. 112. As amended, the language with respect to the cryoprotectant clearly recites that it is present in a concentration effective to raise the glass transition temperature of the vitrification solution or of the cryoprotective equilibration solution and prevent the formation of any ice in that solution. The microdroplets are of the biological materials incorporated in the vitrification solution. This incorporation is realized by the step of rinsing. As to solid surface, what is intended and as now defined is the substantially stationary solid surface onto which the microdroplets of biological material in vitrification solution are deposited. It is this surface which has the recited heat conductivity and which has been cooled also as recited. The method of claim 9 is the method set out at the bottom of page 5 over to page 6 (see also page 7 et seq.). It is a cryopreservation method and starts with the biological material suspended in a vitrification solution. Claim 1 is directed to a method for the vitrification of biological materials and it requires the step of suspending the biological material in a cryoprotective equilibration medium, followed by transfer of the resultant product to a vitrification medium.

The Examiner has rejected all of the claims under 35 U.S.C. 103(a) as being unpatentable over Patent No. 5,780,295 taken with Steponkus et al., Martino et al., Yang et al. and Papis et al. All of these references were known to the applicants and were included in their Information Disclosure Statement as submitted to the Patent Office.

The Examiner has recognized that the cited patent is lacking any teaching with respect to oocytes but he considers that this omission is cured by the teachings of the secondary references. The Examiner has not however considered the very different manner in which the patentee carries out the cooling of the solution of the biological material as taught. Column 4, lines 17, et seq. of the patent clearly recite that cooling of

the solution is achieved by nebulizing the solution to form discrete droplets, said droplets being less than about 200 μm in diameter. The microdroplets are then sprayed onto a rotating cryogenic surface which is internally cooled by a cryogenic fluid to a temperature of less than about -160 °C. The patent always refers to a nebulized cryosolution directed to a continuously replenished cryogenic surface. The use of a nebulizer to deliver a solution as taught involves a gas such as nitrogen, helium, oxygen or argon to prevent precooling. Further the nebulied solution is delivered to a rotating metal surface. As described by the patentee, ice crystal formation takes place but is below the degree that would cause damage to the sample.

The cold surface utilized by the applicants is very different, it is stationary and a substantially solid surface. The method of delivery is different, i.e., droplets of material are supplied directly onto the surface by "dropping" them thereon. The size of the droplets, the nature of the surface, its heat conductivity all contribute to the viability of the oocytes, embryos, etc. .

Further the Examiner has not considered that the materials treated by the patent are "microscopic biological materials "red blood cells, mammalian cultured cells, platelets, leukoocytes, Factor VIII, sperm, pancreatic islets, marrow cells, viruses and vaccines. Suitable materials can be either molecular, viral, bacterial, cellular, or subcellular" (col. 4, lines 56-59), "including tissue fluids" (col. 11, line 25), "cells and tissues", "tissue" (col. 1, lines 33 and 36), "enzymes" (col. 17, line 21) etc. These materials are in each case subjected to nebulization and the nebulized microdroplets frozen. There is furthermore no teaching or suggestion of a critical volume for the droplets ["thin layer of tissues" (Col. 11, line 37), "frozen tissue" (col. 12, line 60) to that the nebulized droplets are less than 200μm in diameter.]

The Steponkus article is concerned with the cryopreservation of insect embryos and larvae. It discloses a number of techniques none of which involve depositing the vitrified insect embryo in direct contact with a stationary plate cooled to -150 °C to -180 °C. Rather polypropylene straws were used which were plunged into liquid propane super cooled with liquid nitrogen, or the eggs contained in the vitrification solution were expelled directly from a syringe, or grids containing the eggs were used in the cooling all at ultra rapid cooling rates. As reported in the article these techniques were more or less effective in minimizing chilling injury to Drosophila embryos. The use of most of these

techniques, if not all has been detailed in the instant specification and have been distinguished from the instant invention.

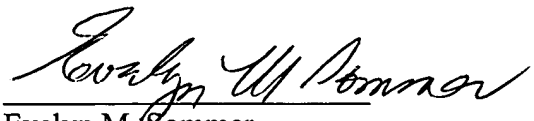
Even if these different starting materials, insect embryos and larvae were used in the 5,780,295 procedure, for all of the reasons stated above, the instant invention would not have been obvious, i.e., the technique, equipment, criticality of droplet size, heat dissipation of the solid stationary surface to which the droplets are transferred would not be suggested.

In the case of Martino et al., the latter represents the state of the art as it has been set forth in the specification. The oocytes are cryopreserved using "straws and grids" (p. 1061). There is no suggestion of the size of the droplets to be used, the likewise of temperatures to be used, the type of equipment, etc. Martino et al's teaching would not be considered by the skilled in the art as a suggestion that bovine oocytes could be used in the procedure taught by the primary reference and even if the artisan would have been so motivated, the claimed technique would not be arrived at or made obvious.
Yang et al. and Papis et al. as stated by the Examiner both involve cryopreserving oocytes. The references each teach rapid cooling of the oocytes. In Yang (also an inventor herein) they (microdrops) were directly dropped into LN_2-filled-Petri dishes floating on LN_2 and in Papis, dropped as droplets directly into LN_2. These techniques are so different that the skilled in the art would not consider their use in the very different procedure of the patent and again, even if this were attempted, the resultant procedure and results would not render the instant invention obvious.

It is noted that both Yang and Papis are entitled to publication dates of 1999. The instant application is entitled to claim priority of two provisional applications dated January 4, 2000 which it is presumed renders the cited references non-available. The application is also entitled to rely on a provisional application of June 30, 2000 which if it were required could be sworn back of under Rule 1.131.

It is submitted that in view of the above, the amended claims are allowable to the Applicants and notice to such effect is now respectfully requested.

Respectfully submitted,



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Version With Markings To Show Changes Made To Paragraph

While not limiting themselves to any particular theory, the present inventors have [opened] opined that the relatively high rates of cryo-survival, and embryo development following vitrification of bovine oocytes can be contributed to several factors. The solid metal surface vitrification method used likely achieves a high cooling rate by the combination of microdrops and improved heat exchange by direct contact with a metal surface. The warming of the oocytes is equally as fast by directly dropping the vitrified samples into a warm solution.

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